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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 535 346 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **02.11.95** (51) Int. Cl.[6]: **C07C 237/26**, A61K 31/65

(21) Application number: **92114054.7**

(22) Date of filing: **18.08.92**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **9-amino-7-substituted-6-demethyl-6-deoxytetracyclines.**

(30) Priority: **04.10.91 US 771697**

(43) Date of publication of application:
07.04.93 Bulletin 93/14

(45) Publication of the grant of the patent:
02.11.95 Bulletin 95/44

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(56) References cited:
DE-A- 2 346 535
US-A- 3 226 436
US-A- 3 338 963
US-A- 3 341 585
US-A- 3 373 198
US-A- 3 397 230

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. L.S GOODMAN ET AL., 5th Edition, MacMillan Publishing Company, New York 1975, page 1183

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EP 0 535 346 B1

Description

1. Field of the Invention

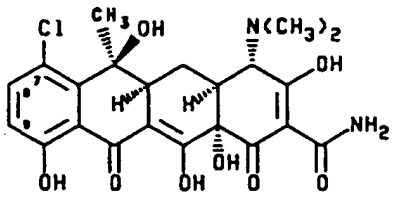
The invention relates to novel [4S-(4α,12aα)]-9-amino-4-(dimethylamino)-7-(substituted amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides, hereinafter called 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as antibacterial agents. The invention also relates to novel 7-(substituted amino)-9-nitro-6-demethyl-6-deoxytetracycline compounds useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

DESCRIPTION OF THE PRIOR ART

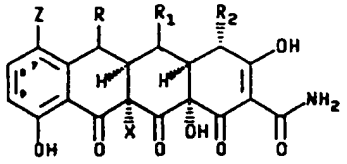
A variety of tetracycline antibiotics have been synthesized and described for the treatment of infectious diseases in man and animals since 1947. Tetracyclines inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome preventing binding of aminoacyl RNA (Chopra, Handbook of Experimental Pharmacology, Vol. 78, 317-392, Springer-Verlag, 1985). Resistance to tetracyclines has emerged among many clinically important microorganisms which limit the utility of these antibiotics. There are two major mechanisms of bacterial resistance to tetracyclines: a) energy-dependent efflux of the antibiotic mediated by proteins located in the cytoplasmic membrane which prevents intracellular accumulation of tetracycline (S. B. Levy, et al., Antimicrob. Agents Chemotherapy 33, 1373-1374 (1989); and b) ribosomal protection mediated by a cytoplasmic protein which interacts with the ribosome such that tetracycline no longer binds or inhibits protein synthesis (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156, 1990). The efflux mechanism of resistance is encoded by resistance determinants designated tetA-tetL. They are common in many Gram-negative bacteria (resistance genes Class A-E), such as Enterobacteriaceae, Pseudomonas, Haemophilus and Aeromonas, and in Gram-positive bacteria (resistance genes Class K and L), such as Staphylococcus, Bacillus and Streptococcus. The ribosomal protection mechanism of resistance is encoded by resistance determinants designated TetM, N and O, and is common in Staphylococcus, Streptococcus, Campylobacter, Gardnerella, Haemophilus and Mycoplasma (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156 1990).

A particularly useful tetracycline compound is 7-(dimethylamino)-6-demethyl-6-deoxytetracycline, known as minocycline (US-A-3,148,212, RE 26,253 and US-A-3,226,436 discussed below). However, strains harboring the tetB (efflux in gram-negative bacteria) mechanism, but not tetK (efflux in Staphylococcus) are resistant to minocycline. Also, strains carrying tetM (ribosomal protection) are resistant to minocycline. This invention describes the synthesis of novel tetracycline compounds which demonstrate significant in vitro and in vivo activity vs. tetracycline and minocycline susceptible strains and some tetracycline and minocycline resistant strains, that is, those harboring the tetM (ribosomal protection) resistance determinants.

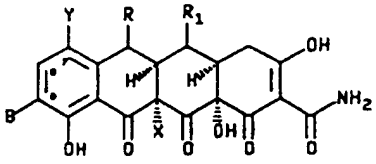
Duggar, US-A-2,482,055, discloses the preparation of Aureomycin® (I) by fermentation which have antibacterial activity. Growich et al., US-A-3,007,965, disclose improvements to the fermentation preparation of I. Neither of these patents teaches or suggests the 6-demethyl-6-deoxytetracyclines.



Beereboom et al., US-A-3,043,875 discloses tetracycline derivatives of the formulae (II) and (III) where R is H or CH_3; R_1 is H and when R is CH_3, OH; R_2 is H and $N(CH_3)_2$; X and Y are halogen; Z is H and halogen and B is bromo, chloro and iodo, which have antibacterial activity. This patent does not teach or suggest the inclusion of both di(lower alkyl)amino or mono(lower alkyl)amino substituents (at Y or Z) and an amino function (at B).

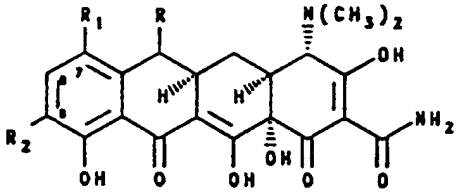


II



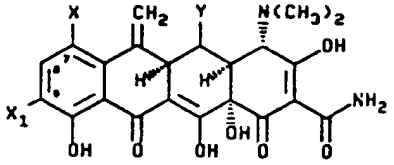
III

Boothe et al., US-A-3,148,212, reissued as RE26,253, and Petisi et al., US-A-3,226,436, discloses tetracycline derivatives of the formula (IV) wherein R is hydrogen or methyl and R_1 and R_2 is hydrogen, mono(lower alkyl)amino or di(lower alkyl)amino with the proviso that R_1 and R_2 cannot both be hydrogen, which are useful for treating bacterial infections. This patent does not teach or suggest the inclusion of a 9-amino functionality (at R_2).

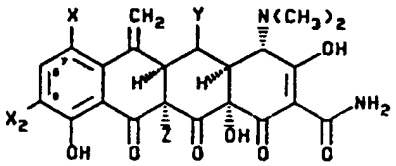


IV

Blackwood et al., US-A-3,200,149 discloses tetracycline derivatives of the formulae (V) and (VI) and reduction products thereof wherein Y may be hydrogen or hydroxyl, X may be hydrogen, chloro, iodo, or bromo, X_1 may be hydrogen, amino, and lower alkanoylamino, X_2 may be hydrogen or nitro and Z is chloro or fluoro which possess microbiological activity. This patent does not teach or suggest the inclusion of both a di(lower alkyl)amino group (at X) and another nitrogen functionality (at X_1) on the 6-demethyl-6-deoxytetracycline nucleus.

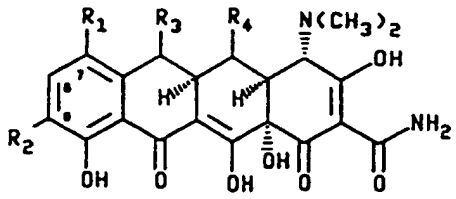


V



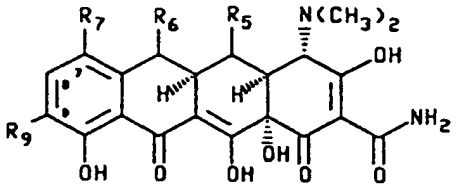
VI

Petisi et al., US-A-3,338,963 discloses tetracycline compounds of the formula (VII) wherein R_1 and R_2 are hydrogen, nitro, amino, formylamino, acetylamino, p-(dihydroxyboryl)benzoylamino, p-(aminobenzenesulfonyl)amino, chlorine, bromine or diazonium with the proviso that R_1 and R_2 may not both be hydrogen and with the further proviso that when R_1 is chlorine or bromine, R_2 may not be hydrogen and vice versa, R_3 is hydrogen or methyl and R_4 is hydrogen or hydroxy, which have broad-spectrum antibacterial activity. This patent does not teach or suggest the inclusion of both di(lower alkyl)amino or mono(lower alkyl)amino substituents (at R_1) and amino substituents (at R_2).



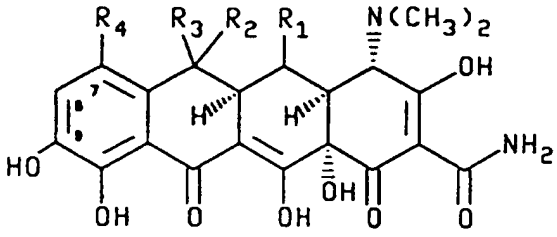
VII

Bitha et al., U.S. Patent No. 3,341,585 discloses tetracycline compounds of the formula (VIII) wherein R_5 is hydrogen, α-hydroxy or β-hydroxy, R_6 is α-methyl or β-methyl, and R_7 and R_9 are each hydrogen, mono-(lower alkyl)amino or di(lower alkyl)amino with the proviso that R_7 and R_9 cannot both be hydrogen and with the further proviso that when R_5 is hydrogen then R_6 is α-methyl. A preferred embodiment of the general formula (VIII) is when R_5 is α-hydroxy or β-hydroxy, R_6 is α-methyl or β-methyl, R_7 is di(lower alkyl)amino and R_9 is hydrogen, which have broad-spectrum antibacterial activity. This patent does not teach or suggest the inclusion of both di(lower alkyl)amino or mono(lower alkyl)amino substituents (at R_7) and amino substituents (at R_9).



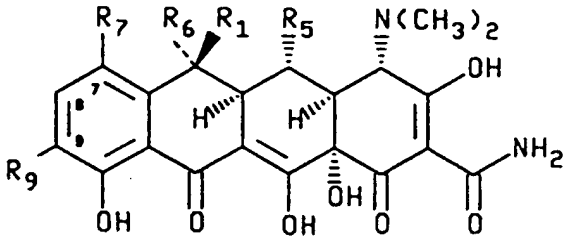
VIII

Shu, US-A-3,360,557 discloses 9-hydroxytetracyclines of the formula (IX) wherein R_1 is hydrogen or hydroxy, R_2 is hydrogen or hydroxy, R_3 is hydrogen or methyl, R_2 and R_3 taken together is methylene, and R_4 is hydrogen, halogen, nitro, amino, mono(lower alkyl)amino or di(lower alkyl)amino, which have been found to possess antibacterial activity. This patent is restricted to 9-hydroxytetracyclines and does not teach or suggest the presently claimed compounds.



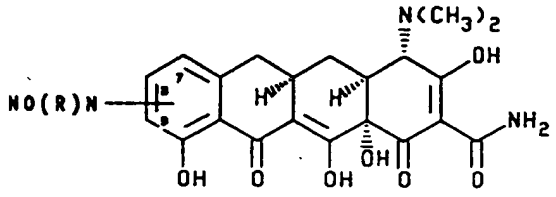
IX

Zambrano, US-A-3,360,561 discloses a process for preparing 9-nitrotetracyclines of the formula (X) wherein R_5 is hydrogen or hydroxy, R_1 is hydrogen or hydroxy, R_6 is hydrogen or methyl, R_1 and R_6 taken together is methylene, R_7 is hydrogen, chloro or nitro and R_9 is hydrogen or nitro with the proviso that R_7 and R_9 cannot both be hydrogen. This patent does not teach or suggest the inclusion of both a di(lower alkyl)amino or mono(lower alkyl)amino substituent (at R_7) and an amino functionality (at R_9).



X

Martell et al., US-A-3,518,306 discloses 7-and/or 9-(N-nitrosoalkylamino)-6-demethyl-6-deoxytetracyclines of the formula (XI) which possess in vivo antibacterial activity. This patent does not teach or suggest the inclusion of both a di(lower alkyl)amino or mono(lower alkyl)amino substituent (at C-7) and an amino functionality (at C-9).



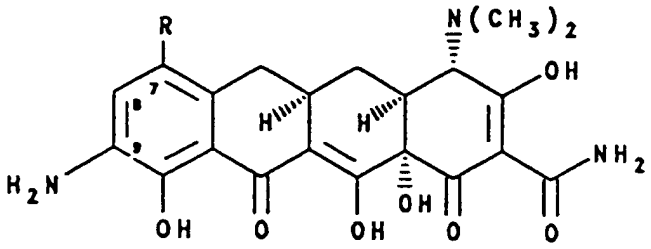
XI

US-A-5,021,407, a method of overcoming the resistance of tetracycline resistant bacteria is disclosed. The method involves utilizing a blocking agent compound in conjunction with a tetracycline type antibiotic. This patent does not disclose novel tetracycline compounds which themselves have activity against resistant organisms.

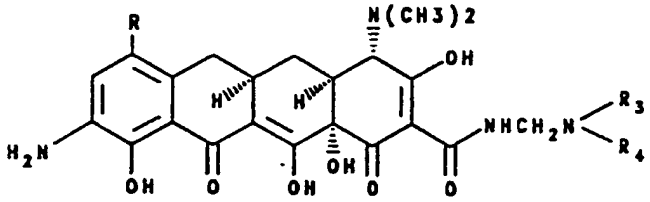
In summary, none of the above patents teach or suggest the novel compounds of this application. In addition, none of the above patents teach or suggest novel tetracycline compounds having activity against tetracycline and minocycline resistant strains as well as strains which are normally susceptible to tetracyclines.

SUMMARY OF THE INVENTION

This invention is concerned with novel 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclines, represented by formula I and II, which have antibacterial activity, with methods of treating infectious diseases in warm-blooded animals employing these new compounds; with methods of treating or controlling veterinary diseases; with pharmaceutical preparations containing these compounds; with novel intermediate compounds and processes for the production of these compounds. More particularly, this invention is concerned with compound of formula I which have enhanced in vitro and in vivo antibacterial activity against tetracycline resistant strains as well as a high level of activity against strains which are normally susceptible to tetracyclines.



Formula I



Formula II

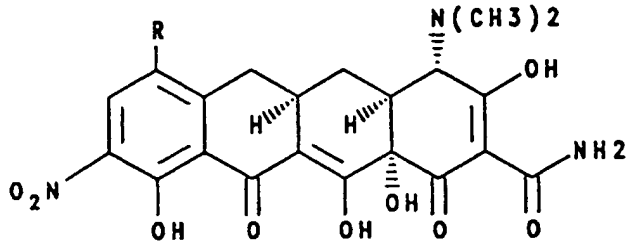
In formula I and II, R = NR_1R_2, and when R_1 = hydrogen, R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R_1 = methyl or ethyl,
R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = n-propyl,
R_2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = 1-methylethyl,
R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = n-butyl,
R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = 1-methylpropyl,
R_2 = 2-methylpropyl;
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$-$COOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group such as phenyl, α-naphthyl, β-naphthyl; R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$-$COOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl such as phenyl, α-naphthyl or β-naphthyl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts, and metal complexes.

Particularly preferred are compounds according to the above formula I and II in which R = NR_1R_2,
and when R_1 = hydrogen,
R_2 = ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

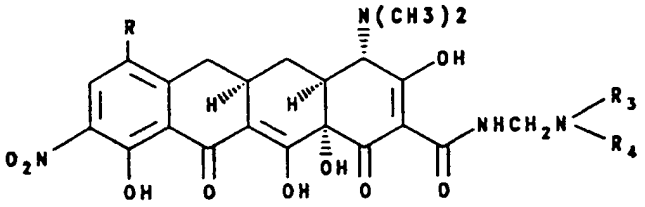
and when R_1 = methyl,
R_2 = methyl, ethyl, n-propyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = ethyl,
R_2 = ethyl, n-propyl, n-butyl or 2-methylpropyl;
and when R_1 = n-propyl,
R_2 = n-propyl, n-butyl or 2-methylpropyl;
and when R_1 = n-butyl,
R_2 = n-butyl or 2-methylpropyl;
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$-$COOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group such as phenyl, α-naphthyl, β-naphthyl;
R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$-$COOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl such as phenyl, α-naphthyl or β-naphthyl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-,wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts, and metal complexes.

Most particularly preferred are compounds according to the above formula I and II in which
R = NR_1R_2,
and when R_1 = hydrogen,
R_2 = ethyl, n-propyl or 1-methylethyl;
and when R_1 = methyl,
R_2 = methyl, ethyl or n-propyl; and
when R_1 = ethyl,
R_2 = ethyl;
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$-$COOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group such as phenyl, α-naphthyl, β-naphthyl;
R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$-$COOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl such as phenyl, α-naphthyl or β-naphthyl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-,wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts, and metal complexes.

Also included in the present invention are compounds useful as intermediates for producing the above compounds of formula I. Such intermediate compounds include those having the formulae:



Formula III



Formula IV

wherein:
$R = NR_1R_2$,
and when R_1 = hydrogen,
R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R_1 = methyl or ethyl,
R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = n-propyl,
R_2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = 1-methylethyl,
R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = n-butyl,
R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = 1-methylpropyl,
R_2 = 2-methylpropyl;
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $-(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group such as phenyl, α-naphthyl, β-naphthyl;
R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $-(CH_2)_nCOOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl such as phenyl, α-naphthyl or β-naphthyl; or R_3 and R_4 taken together are $-(CH_2)_2W(CH_2)_2-$,wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts, and metal complexes.

Particularly preferred are compounds according to the above formula III and IV in which $R = NR_1R_2$, and when R_1 = hydrogen,

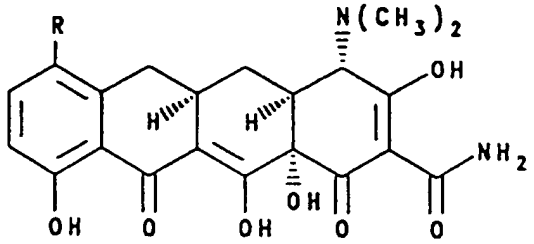
R_2 = ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R_1 = methyl,
R_2 = methyl, ethyl, n-propyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = ethyl,
R_2 = ethyl, n-propyl, n-butyl or 2-methylpropyl;
and when R_1 = n-propyl,
R_2 = n-propyl, n-butyl or 2-methylpropyl;
and when R_1 = n-butyl,
R_2 = n-butyl or 2-methylpropyl;
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$COOR$_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group such as phenyl, α-naphthyl, β-naphthyl;
R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$COOR$_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl such as phenyl, α-naphthyl or β-naphthyl; or R_3 and R_4 taken together are -$(CH_2)_2$W$(CH_2)_2$-,wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts, and metal complexes.

Most particularly preferred are compounds according to the above formula III and IV in which R = NR$_1$,R$_2$, and when R_1 = hydrogen,
R_2 = ethyl, n-propyl or 1-methylethyl;
and when R_1 = methyl,
R_2 = methyl, ethyl or n-propyl;
and when R_1 = ethyl,
R_2 = ethyl;
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$COOR$_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group such as phenyl, α-naphthyl, β-naphthyl;
R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group such as methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group such as phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group such as 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$COOR$_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl such as methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl such as phenyl, α-naphthyl or β-naphthyl; or R_3 and R_4 taken together are -$(CH_2)_2$W$(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from
(L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts, and metal complexes.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The novel compounds of the present invention may be readily prepared in accordance with the following schemes.

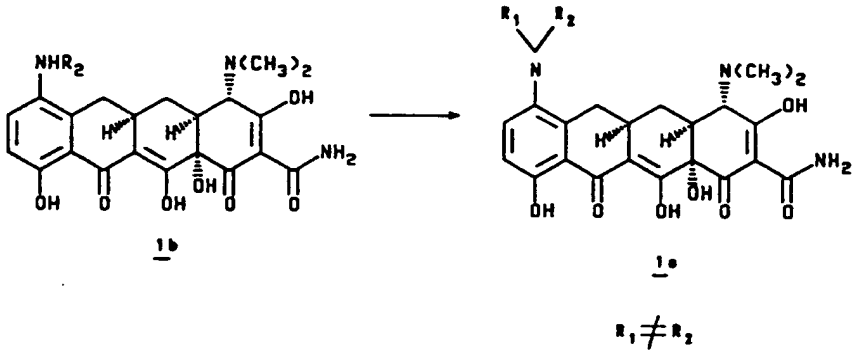
The starting 7-(substituted amino)-6-demethyl-6-deoxytetracyclines described in formula 1, wherein R = NR$_1$R$_2$ and R_1 = R_2 (1a) and R = NHR$_2$ (1b) or the salts thereof are prepared by procedures known to those skilled in the art including those described in U.S. Patents 3,226,436 and 3,518,306.



1a = R = NR_1R_2, $R_1 = R_2$
1b = R = NHR_2
1c = R = NR_1R_2, $R_1 \neq R_2$

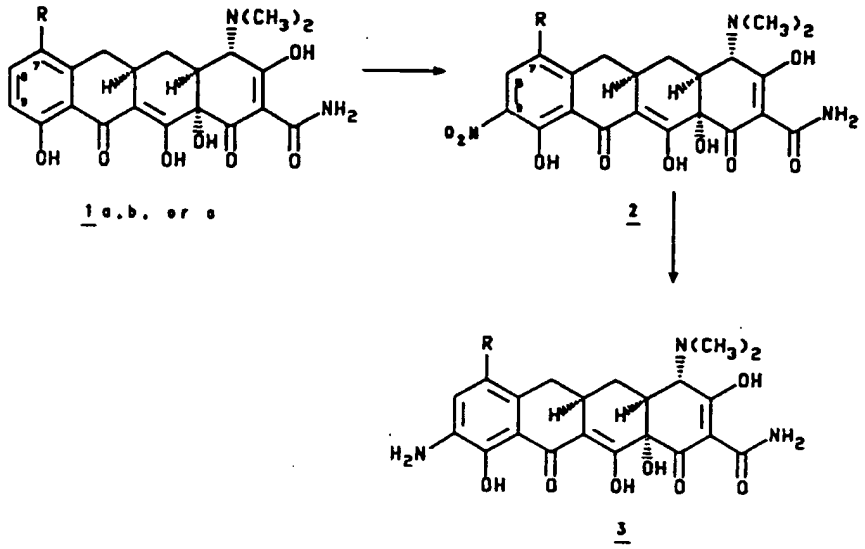
The starting 7-(substituted amino)-6-demethyl-6-deoxytetracyclines described in formula 1 wherein R = NR_1R_2 and $R_1 \neq R_2$ (1c) are prepared according to Scheme 1.

Scheme I



In accordance with Scheme I, a 7-(monoalkylamino)-6-demethyl-6-deoxytetracycline, 1b, in which R = NHR_2, is reductively alkylated with an aldehyde to give an unsymmetrical dialkylamino, 1c.

Scheme II



In accordance with Scheme II, a 7-(substituted amino)-6-demethyl-6-deoxytetracycline or its salts, 1a-1c, is treated with

a) a metal nitrate salt; such as calcium, potassium or sodium; and a strong acid; such as sulfuric acid, trifluoroacetic acid, methanesulfonic acid or perchloric acid or

b) nitric acid and a strong acid; such as sulfuric acid, trifluoroacetic acid, methanesulfonic acid or perchloric acid; to form the corresponding 7-(substituted amino)-9-nitro-6-demethyl-6-deoxytetracycline 2.

To produce the 9-(amino)-7-(substituted amino)-6-demethyl-6-deoxytetracyclines of the present invention, compound 2 or its salts is treated with hydrogen in an acid alcohol solvent, preferably 2-methoxyethanol, in the presence of a suitable catalyst such as, for example:

a) any supported catalyst; such as 0.5-25% palladium-on-carbon, 0.5-25% palladium-on-barium sulfate, 0.5-25% platinum-on-carbon or 0.5-25% rhodium-on-carbon;

b) any reducible metal oxide catalyst; such as Raney nickel or platinum oxide; or

c) a homogeneous hydrogenation catalyst; such as tris(triphenylphosphine)rhodium (I) chloride; to obtain the 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracycline, 3.

Alternatively, the 9-(amino)-7-(substituted amino)-6-demethyl-6-deoxytetracyclines of the present invention are obtained by treating with:

a) stannous chloride dihydrate as described by R. B. Wordward, Org. Syn., Coll. Vol. 3, 453 (1955);

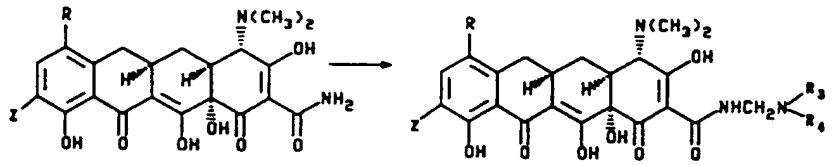
b) a soluble metal sulfide, preferably sodium sulfide, in alcoholic solvents as described by G. R. Robertson, Org. Syn., Coll. Vol. 1, 52 (1941);

c) an active metal in mineral acid; such as iron, tin or zinc in dilute hydrochloric acid;

d) active metal couples; such as copper-zinc, tin-mercury or aluminum amalgam in dilute acid; or

e) transfer hydrogenation using triethylammonium formate and a supported catalyst as described by I. D. Entwistle et al., J. Chem. Soc., Perkin 1, 443 (1977).

Scheme III



4 5

In accordance with Scheme III, Z = NO_2 or NH_2; compound 4 is selectively N-alkylated in the presence of formaldehyde and either a primary amine such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or D) lysine, (L or D) alanine or their substituted congeners; or a secondary amine such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adducts, 5, of the biologically active 7-(substituted amino)-6-demethyl-6-deoxytetracyclines. Contemplated equivalents include those substituted morpholine, pyrrolidine or piperidine moieties wherein the substituents are chosen to provide the requisite increase in solubility without adversely affecting antibacterial activity.

The 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclines, 3, may also be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art. Preferably, the 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclines, are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate. In all cases, the salt formation occurs with the C(4)-dimethylamino group. The salts are preferred for oral and parenteral administration.

Biological Activity

Methods for In Vitro Antibacterial Evaluation (Table 1)

The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth of the test organism, is determined by the microtiter broth dilution method using 0.1 ml Muller-Hinton II broth (Baltimore Biological Laboratories) per well. A suitable oxygen scavenger (i.e., cysteine or dithiothreitol) is added to the assay medium for the testing of compounds according to Formula I because of the sensitivity of those compounds to oxidation. An inoculum level of 1-5 x 10^5 CFU/ml and a range of antibiotic concentrations (32 -0.004 µg/ml) are used. MIC's were determined after the plates were incubated for 18 hours at 35 °C in a forced air incubator.

E. coli in vitro protein translation system (Table 2)

The E. coli in vitro translation system can be used to study not only the mechanism of protein translation itself, but also the effect that various compounds may have on protein synthesis. The system can be set up to function as a coupled transcription and translation system or as a translation only system depending on whether DNA or RNA is added to initiate protein synthesis. In this way, compounds affecting either RNA synthesis and/or protein synthesis can be studied. Protein synthesis is monitored by the incorporation of radiolabeled amino acids into trichloroacetic acid precipitable material. The system used is based upon literature methods [G. Zubay, Ann. Rev. Genet., 7: 267-287(1973) and J. Collins, Gene, 6: 28-42 (1979)].

The system used to study tetracycline protein synthesis inhibition is as follows:

An S30 extract (supernatant from a 30,000 x G centrifugation of lysed cells) of either tetracycline

sensitive or tetracycline resistant (tetM+) cells is combined with a mixture of low molecular weight compounds required for protein synthesis which include a mixture of 19 amino acids, methionine, ^{35}S-methionine, plasmid template DNA and either dimethylsulfoxide (DMSO) or the tetracycline to be tested dissolved and diluted in DMSO. This mixture is incubated at 37°C for 30 minutes. Following the incubation, 2.5 µl of the 10 µl reaction is removed and added to 0.5 ml of 1N sodium hydroxide. The solution is incubated an additional 15 minutes at 37°C, to destroy any m-RNA and t-RNA. The incorporation of ^{35}S-methionine is determined by precipitating the high molecular weight material in the sodium hydroxide aliquot with trichloroacetic acid (TCA), collecting the precipitated material on Whatman G/FC filters, drying the filters and counting the radioactivity retained on the filter. Percent inhibition (P.I.) of protein synthesis is determined by the following equation:

$$P.I. = 100 - \left(\frac{\text{total CPM* retained on filter in the presence of added tetracycline compound}}{\text{Total CPM* retained on filter for DMSO (control)}} \right) X100$$

*CPM = counts per minute

In Vivo Antibacterial Evaluation (Table 3)

The therapeutic effects of tetracyclines are determined against acute lethal infections with various staphylococcal and E. coli strains. Female mice, strain CD-1 Charles River Laboratories, (20 ± 2 grams) are challenged by an intraperitoneal injection of sufficient bacteria (suspended in broth or hog gastric mucin) to kill non-treated controls within 24-48 hours. Antibacterial agents, contained in 0.5 ml of 0.2% aqueous agar, are administered subcutaneously or orally 30 minutes after infection. When an oral dosing schedule is used, animals are deprived of food for 5 hours before and 2 hours after infection. Five mice are treated at each dose level. The 7 day survival ratios from three separate tests are pooled for calculation of median effective dose (ED_{50}).

Legend for Tables I - III

A = 9-Amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride
B = 7-(Dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (minocycline hydrochloride)
C = 9-Amino-7-(diethylamino)-6-demethyl-6-deoxytetracycline sulfate
D = 7-(Diethylamino)-6-demethyl-6-deoxytetracycline sulfate

Table 1

In Vitro Antibacterial Activity of 6-Demethyl-6-deoxytetracycline Derivatives

Organism*	MIC (µg/ml) A[a]	B	C[a]	D
S. aureus UBMS 88-5 (*tetM*)	0.06	4	0.5	16
S. aureus UBMS 88-4 (tetracycline-sensitive)	0.015	0.008	0.03	0.03
S. aureus UBMS 90-1 (*tetM*)	0.25	4	2	8
S. aureus UBMS 90-2 (*tetM*)	0.06	1	0.25	8
S. aureus UBMS 90-3 (tetracycline-sensitive)	0.015	0.015	0.03	0.03
S. aureus UBMS 88-7 (*tetK*)	0.12	0.03	0.06	0.12
S. aureus IVES 2943 (methicillin-resistant)	0.5	1	0.25	8
S. aureus IVES 1983 (methicillin-resistant)	0.5	1	0.25	8
S. aureus CI 2371 (methicillin-resistant)	0.5	4	NA	NA
S. aureus CI3300 (methicillin-resistant)	0.25	8	NA	NA
Coagulase negative staphylococci CI 664	0.003	0.015	NA	NA
Coagulase negative staphylococci CI 535	1	8	NA	NA
S. haemolyticus AVAH 88-3	0.06	0.12	0.12	NA
E. faecalis AMV 120 (*tetM*)	4	16	NA	NA
E. faecalis PAM 211 (*tetN*)	4	16	NA	NA
E. faecalis 12201 (vancomycin-resistant)	0.5	4	NA	NA
E. faecalis CI 2735	0.5	4	NA	NA
E. coli UBMS 88-1 (*tetB*)	>32	8	2	32
E. coli UBMS 88-2 (tetracycline-sensitive)	0.25	0.5	0.5	2
E. coli UBMS 89-1 (*tetM*)	1	8	2	NA
E. coli UBMS 89-2 (tetracycline-sensitive)	0.5	0.5	0.5	4
E. coli UBMS 90-4 (*tetM*)	4	>32	32	>32
E. coli UBMS 90-5 (tetracycline-sensitive)	0.25	0.5	1	2
M. morganii NEMC 87-119	2	2	2	32
S. marcescens FPOR 87-33	4	2	4	32
P. aeruginosa ATCC 27853	2	4	8	32
X. maltophilia FPOR 87-210	0.12	0.06	0.12	0.25
E. coli ATCC25922	0.25	0.25	0.50	1
E. faecalis ATCC 29212	0.06	0.25	0.12	8
S. aureus ATCC 29213	0.008	≤0.004	≤0.015	<0.015

[a] *In vitro* assay is done in the presence of cysteine (0.05%). Antibacterial potency of B and D was not enhanced in the presence of cysteine.

* The *tetM* resistance determinant protects ribosomes from tetracycline, the *tetK* determinant promotes efflux of the drug from the cell.

Table 2. *In Vitro* Protein Translation with *E. coli* S30 Ribosomes

Wild Type Version

	B				A			
	Wild Type S30 no DTT*		Wild Type S30 with DTT*		Wild Type S30 no DTT*		Wild Type S30 with DTT	
Reaction	Counts	% Inhibition	Counts	% Inhibition	Counts	% Inhibition	Counts	% Inhibitior
Control DMSO	457268		872132		457268		872132	
Plus compound								
1.0 mg/ml	57696	87	58885	93	52595	88	38121	96
1:2 Dilution	76804	83	78961	91	80494	82	60891	93
1:4 Dilution	53400	88	111971	87	95015	79	92203	89
1:8 Dilution	162405	64	149792	83	130209	72	143215	84
1:16 Dilution	213077	53	207484	76	205392	55	214831	75
1:32 Dilution	306650	33	289304	67	297786	35	238321	73
1:64 Dilution	457601	0	518601	41	245494	46	380103	56

tetM Variant

	tetM S30 no DTT*		*tetM* S30 with DTT*		*tetM* S30 no DTT*		*tetM* S30 with DTT*	
Reaction	Counts	% Inhibition	Counts	% Inhibition	Counts	% Inhibition	Counts	% Inhibitior
Control DMSO	247938		447247		247938		447247	
Plus compound								
1.0 mg/ml	281528	0	371475	17	129780	48	145068	68
1:2 Dilution	258633	0	331439	26	158861	36	168574	62
1:4 Dilution	248904	0	373168	17	203184	18	226708	49
1:8 Dilution	289595	0	421533	6	231447	7	284606	36
1:16 Dilution	287498	0	493679	0	305633	0	375989	16
1:32 Dilution	262329	0	490283	0	349994	0	412967	8
1:64 Dilution	249242	0	452837	0	310723	0	507461	0

*Dithiothreitol (DTT) is used as an oxygen scavenger.

EP 0 535 346 B1

Table 3

Effects of Compounds A and B on Acute Lethal Infections in Mice			
Organism	Route of Antibiotic Administration*	ED_{50} (mg/kg)+	
		A	B
E. coli 311 (sens)	Subcutaneous	2.8	3.1
E. coli UBMS 90-4 (*tet*M)	Subcutaneous	24	>256
S. aureus UBMS 90-1 (*tet*M)	Subcutaneous	0.30	1.7
S. aureus UBMS 90-2 (*tet*M)	Oral	1.6	1.8
	Subcutaneous	0.53	1.8
S. aureus Smith (sens)	Oral	0.81	0.53
	Subcutaneous	0.34	0.32

* Single Dose

+ Median effective dose protecting 50% of the infected mice

Testing Results

As seen from the above testing, the compounds according to the present invention display good activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially strains of E. coli, S. aureus and E. faecalis containing the tetM or tetK resistant determinants. As illustrated in Table I, 9-amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (A) shows good in vitro activity against tetracycline resistant strains carrying the tetM resistance determinant such as S. aureus UBMS 88-5, S-aureus UBMS 90-1 and 90-2, E. coli UBMS 89-1 and 90-4; and is equally as effective as 7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (B) vs. susceptible strains. 7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (B) and 9-amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (A) are assayed in vitro for their ability to inhibit protein synthesis, taking place on either wild type or tetM protected ribosomes, using a coupled transcription and translation system. Similarly, 9-amino-7-(diethylamino)-6-demethyl-6-deoxytetracycline sulfate (C) shows enhancement of antibacterial activity versus 7-(diethylamino)-6-demethyl-6-deoxytetracycline sulfate (D).

Both compounds (A & B) are found to effectively inhibit protein synthesis on wild type ribosomes, having equivalent levels of activity (Table II). 7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (B) is unable to inhibit protein synthesis occurring on tetM protected ribosomes. In contrast, 9-amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (A) is effective in inhibiting protein synthesis occurring on tetM protected ribosomes, although higher drug levels are required to achieve similar levels of inhibition relative to wild type ribosomes.

The enhanced activity of 9-amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline sulfate (A) against tetracycline susceptible and resistant organisms (tetM) is demonstrated in Table 3 for animals infected with representative bacteria. Lowered ED_{50}'s are obtained with 9-amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline sulfate (A) than with 7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (B) in mice with of S. aureus and E. coli which carry the tetM resistance determinant. Similar ED_{50}'s are obtained with 9-amino-7-(dimethylamino)-6-demethyl-6-deoxytetracycline sulfate (A) and 7-(dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (B) against infections with minocycline susceptible organisms.

As can be seen from Tables 1 and 3, the new 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclines may be used to prevent or control important veterinary diseases such as mastitis, diarrhea, urinary tract infections, skin infections, ear infections, wound infections and the like.

The improved efficacy of the new 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclines is evidenced by the in vitro activity against isogenic strains into which the resistant determinants, such as tetM, were cloned (Table 1); the inhibition of protein synthesis by tetM resistant ribosomes (Table 2); and the in vivo activity against experimental infections caused by strains resistant to the tetracyclines, due to the presence of resistant determinants, tetM (Table 3).

When the compounds are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for

example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

An effective amount of compound from 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should be administered one to four times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The invention will be more fully described in conjunction with the following specific examples which are not to be construed as limiting the scope of the invention.

Example 1

[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

To a stirred ice bath cooled solution of 0.444 g of [4S-(4α,12aα)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride, prepared by the procedure described in U.S Patent 3,226,436, dissolved in 15 ml of sulfuric acid is added 0.101 g of sodium nitrate. The mixture is stirred in the cold for 45 minutes followed by the dropwise addition to 500 ml of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.6 g of the desired product as a solid. MS(FAB): m/z 503(M + H) and 601(M + H_2SO_4 + H).

Example 2

[4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2)

To a stirred ice cooled solution of 0.660 g of [4S-(4α,12aα)]-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride, prepared by the procedure described in U.S. Patent 3,226,436, dissolved in 15 ml of sulfuric acid is added 0.151 g of sodium nitrate. The mixture is stirred in the cold followed by dropwise addition to 500 ml of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.8 g of the desired product as a solid. MS(FAB): m/z 531(M + H) and 629(M + H_2SO_4 + H).

Example 3

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

A mixture of 2.0 g of product from Example 1 in 20 ml of 2-methoxyethanol is stirred for 10 minutes and filtered. The filtrate is shaken, in a pressure bottle, with 1.0 g of 10% palladium-on-carbon and 5 ml of 2N sulfuric acid, under 30 lbs. of hydrogen pressure, for 1 hour. The reaction mixture is filtered and the filtrate concentrated in vacuo to half volume. The solution is poured into 100 ml of diethyl ether, the solid collected, washed with diethyl ether and dried to give 1.6 g of the desired product as a solid. MS(FAB): m/z 473(M + H).

Example 4

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12α-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1)

A mixture of 20.0 g of product from Example 1 in 250 ml of 2-methoxyethanol is stirred for 10 minutes and filtered. The filtrate is shaken, in a pressure bottle, with 10.0 g of 10% palladium-on-carbon and 100 ml of 1N ethanolic hydrogen chloride, under 30 lbs. of hydrogen pressure, for 1 hour. The reaction mixture is filtered and the filtrate concentrated in vacuo to half volume. The solution is poured into 1 L of diethyl ether, the solid collected, washed with diethyl ether and dried to give 16.0 g of the desired product as an oil. The oil is suspended in 20 ml of distilled water, made acidic with 2.8 ml of 32% hydrochloric acid and decolorized with charcoal. The mixture is filtered through diatomaceous earth and made basic (pH 4.0) with concentrated ammonium hydroxide. The solid is collected at 4 °C, washed with pH 4 water and dried in vacuo to give 14.2 g of the desired product as a solid.
^{1}H NMR (CD_3SOCD_3): δ 4.19(s,1H,4-H) and 7.29(s,1H,8-H).
MS(FAB): m/z 473(M + H).

Analysis for $C_{23}H_{28}N_4O_7$ HCl 6.7% H_2O				
Calc'd:	C,50.64;	H,6.10;	N,10.27;	Cl,6.50
Found:	C,50.72;	H,6.07;	N,10.27;	Cl,6.62.

Example 5

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide p-toluenesulfonate (1:1)

The title compound is prepared by the procedure of Example 4, using 20 g of product from Example 1, to give 16.0 g of the desired product as the free base. The free base is suspended in 20 ml of distilled water, made acidic with p-toluenesulfonic acid monohydrate and decolorized with charcoal. The mixture is filtered through diatomaceous earth and made basic (pH 4.0) with concentrated ammonium hydroxide. The solid is collected at 4 °C, washed with pH 4 water and dried in vacuo to give 16.0 g of the desired product.

Example 6

[4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2)

The title compound is prepared by the procedure of Example 3, using 2.1 g of product from Example 2, to give 1.5 g of the desired product as a solid. ^{1}H NMR (CD_3SOCD_3): δ 4.25(s,1H,4-H) and 7.27(s,1H,8-H). MS(FAB): m/z 501(M + H) and 599(M + H_2SO_4 + H).

Example 7

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1)

A solution of 0.460 g of [4S-(4α,12aα)]-4-(dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride, prepared by the procedure described in US-A-3,226,436, 0.5 ml of 97% formic acid and 0.75 ml of 40% aqueous formaldehyde is heated at reflux temperature for 2 hours. The reaction mixture is cooled, concentrated in vacuo to half volume and poured into diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.3 g of the desired product as a solid.

Example 8

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

The title compound is prepared by the procedure of Example 1, using 0.46 g of product from Example 7 to give 0.5 g of the desired product as a solid.

Example 9

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethylmethylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

The title compound is prepared by the procedure of Example 3, using 1.0 g of product from Example 8, to give 0.8 g of the desired product as a solid.

Example 10

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

The title compound is prepared by the procedure of Example 1, using 0.48 g of [4S-(4α,12aα)]-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride, prepared by the procedure described in U.S. Patent 3,226,436, to give 0.5 g of the desired product as a solid.

Example 11

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

The title compound is prepared by the procedure of Example 3, using 2.1 g of product from Example 10, to give 1.5 g of the desired product as a solid.

Example 12

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

The title compound is prepared by the procedure of Example 1, using 0.96 g of [4S-(4α,12aα)]-4-(dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide prepared by the procedure described in US-A-3,226,436, to give 0.9 g of the desired product as a solid.

Example 13

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

The title compound is prepared by the procedure of Example 3, using 1.0 g of product from Example 12, to give 0.7 g of the desired product as a solid.

Examples 14-35

Substantially following the methods described in detail hereinabove in Examples 3 and 9, the compounds of this invention listed below in Examples 14-35 are prepared.

Example 14

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(methylpropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 15

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(butylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 16

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[1-methylpropylamino)methylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 17

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(2-methylpropyl)methylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 18

[4S-(4α,12aα))]-9-Amino-4-(dimethylamino)-7-(ethylpropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 19

[4S-(4α,12aα))]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 20

[4S-(4α,12aα))]-9-Amino-4-(dimethylamino)-7-(butylethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 21

[4S-(4α,12aα))]-9-Amino-4-(dimethylamino)-7-[(1-methylpropyl)ethylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 22

[4S-(4α,12aα))]-9-Amino-4-(dimethylamino)-7-[(2-methylpropyl)ethylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 23

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(dipropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 24

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methyethyl)propylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 25

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(butylpropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 26

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylpropyl)propylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 27

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(2-methylpropyl)propylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 28

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)butylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 29

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)(1-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 30

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)(2-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 31

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(dibutylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 32

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylpropyl)butylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 33

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(2-methylpropyl)butylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 34

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 35

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylpropyl)(2-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro -3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Examples 36-39

Substantially following the methods described in detail hereinabove in Examples 3 and 11, the compounds of this invention listed below in Examples 36-39 are prepared.

Example 36

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(propylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 37

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(butylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 38

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(2-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 39

[4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1,1-dimethylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Examples 40-65

Substantially following the methods described in detail hereinabove in Examples 1 and 2, the compounds of this invention listed below in Examples 40-65 are prepared.

Example 40

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(methylpropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 41

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(butylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 42

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylpropylamino)methylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 43

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(2-methylpropyl)methylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 44

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylpropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 45

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 46

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(butylethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 47

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylpropyl)ethylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 48

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(2-methylpropyl)ethylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 49

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(dipropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 50

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)propylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate

Example 51

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(butylpropylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 52

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylpropyl)propylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 53

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(2-methylpropyl)propylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 54

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)butylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 55

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)(1-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 56

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)(2-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 57

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(dibutylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 58

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylpropyl)butylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 59

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(2-methylpropyl)butylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 60

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 61

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylpropyl)(2-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 62

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(propylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 63

[4S-(4α,12aα)]-4-(Dimethylamino)-7-(butylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

Example 64

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(2-methylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

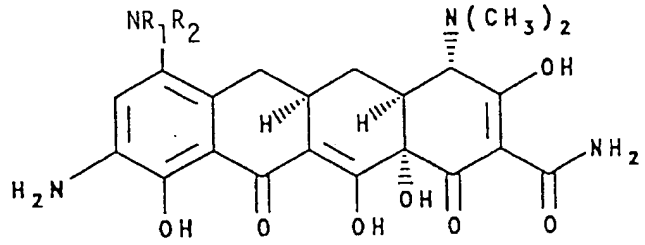
Example 65

[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1,1-dimethylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate.

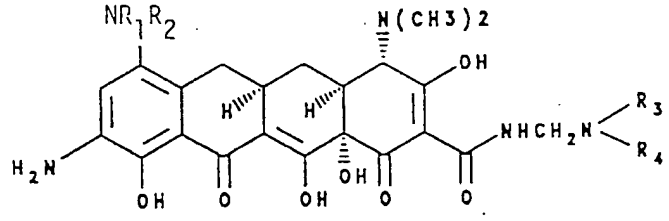
Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IE, IT, LI, LU, NL, PT, SE

1. A compound of the formula (I) or (II):



(I)



(II)

wherein:

when R_1 = hydrogen,

R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R_1 = methyl or ethyl,

R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = n-propyl,

R_2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = 1-methylethyl,

R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = n-butyl,

R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = 1-methylpropyl,

R_2 = 2-methylpropyl;

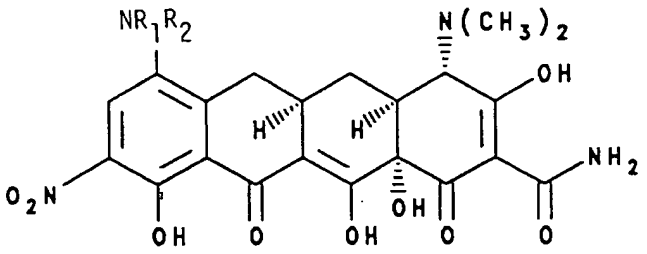
R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)-aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-

C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; or (C_6-C_{10})aryl group;
R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)-aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_nCOOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl; or (C_6-C_{10})aryl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from
(L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.

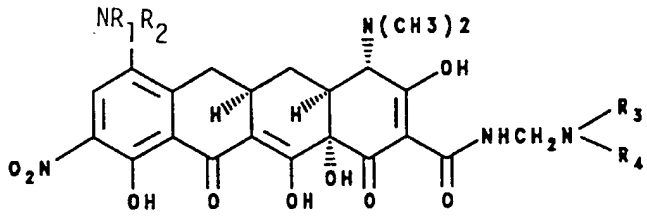
2. The compound according to Claim 1, wherein:
when R_1 = hydrogen,
R_2 = ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and
when R_1 = methyl,
R_2 = methyl, ethyl, n-propyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R_1 = ethyl,
R_2 = ethyl, n-propyl, n-butyl, or 2-methylpropyl;
and when R_1 = n-propyl,
R_2 = n-propyl, n-butyl or 2-methylpropyl;
and when R_1 = n-butyl,
R_2 = n-butyl or 2-methylpropyl;
R_3 is selected from straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; or (C_6-C_{10})aryl group;
R_4 is selected from straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_nCOOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl; or (C_6-C_{10})aryl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)-alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline or ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.

3. The compound according to Claim 1, wherein:
when R_1 = hydrogen,
R_2 = ethyl, n-propyl or 1-methylethyl;
and when R_1 = methyl;
R_2 = methyl, ethyl or n-propyl;
and when R_1 = ethyl;
R_2 = ethyl;
R_3 is selected from a straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)aralkyl group; or -$(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; or (C_6-C_{10})aryl group;
R_4 is selected from straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)aralkyl group; or -$(CH_2)_nCOOR_6$ when n = 1-4
R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl; or (C_6-C_{10})aryl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline or ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.

4. A compound of the formula (I) or (II):



(I)



(II)

wherein:

when R_1 = hydrogen,

R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R_1 = methyl or ethyl,

R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = n-propyl,

R_2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = 1-methylethyl,

R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = n-butyl,

R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = 1-methylpropyl,

R_2 = 2-methylpropyl;

R_3 is selected from hydrogen, straight or branched (C_1--C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)-aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$$COOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; or (C_6-C_{10})aryl group;

R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)-aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or -$(CH_2)_n$$COOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl; or (C_6-C_{10})aryl; or R_3 and R_4 taken together are -$(CH_2)_2W(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from

(L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.

5. The compound according to Claim 4, wherein

when R_1 = hydrogen,

R_2 = ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R_1 = methyl,

R_2 = methyl, ethyl, n-propyl, n-butyl, 1-methylpropyl, or 2-methylpropyl;

and when R_1 = ethyl,
R_2 = ethyl, n-propyl, n-butyl, or 2-methylpropyl;
and when R_1 = n-propyl,
R_2 = n-propyl, n-butyl, or 2-methylpropyl;
and when R_1 = n-butyl,
R_2 = n-butyl or 2-methylpropyl;
R_3 is selected from straight or branched $(C_1\text{-}C_3)$alkyl group; $(C_6\text{-}C_{10})$aryl group; $(C_7\text{-}C_9)$aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di$(C_1\text{-}C_3)$alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched $(C_1\text{-}C_3)$alkyl group; or $(C_6\text{-}C_{10})$aryl group;
R_4 is selected from straight or branched $(C_1\text{-}C_3)$alkyl group; $(C_6\text{-}C_{10})$aryl group; $(C_7\text{-}C_9)$aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di$(C_1\text{-}C_3)$alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $-(CH_2)_nCOOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched $(C_1\text{-}C_3)$alkyl; or $(C_6\text{-}C_{10})$aryl; or R_3 and R_4 taken together are $-(CH_2)_2W(CH_2)_2-$, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N$(C_1\text{-}C_3)$alkyl, -N$(C_1\text{-}C_4)$-alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline or ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.
$(C_1\text{-}C_3)$alkyl; $(C_6\text{-}C_{10})$aryl; or R_3 and R_4 taken together are $-(CH_2)_2W(CH_2)_2-$, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N$(C_1\text{-}C_3)$alkyl, -N$(C_1\text{-}C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.

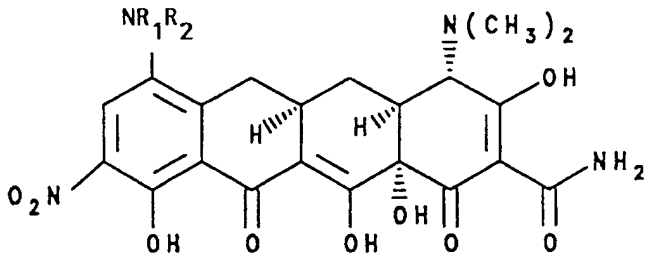
6. The compound according to Claim 4, wherein:
when R_1 = hydrogen,
R_2 = ethyl, n-propyl or 1-methylethyl;
and when R_1 = methyl,
R_2 = methyl, ethyl or n-propyl;
and when R_1 = ethyl,
R_2 = ethyl;
R_3 is selected from a straight or branched $(C_1\text{-}C_3)$alkyl group; $(C_6\text{-}C_{10})$aryl group; $(C_7\text{-}C_9)$aralkyl group; or $-(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched $(C_1\text{-}C_3)$alkyl group; or $(C_6\text{-}C_{10})$aryl group;
R_4 is selected from straight or branched $(C_1\text{-}C_3)$alkyl group; $(C_6\text{-}C_{10})$aryl group; $(C_7\text{-}C_9)$aralkyl group; or $-(CH_2)_nCOOR_6$ when n = 1-4 and
R_6 is selected from hydrogen; straight or branched $(C_1\text{-}C_3)$alkyl; or $(C_6\text{-}C_{10})$aryl; or R_3 and R_4 taken together are $-(CH_2)_2W(CH_2)_2-$, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N$(C_1\text{-}C_3)$alkyl, -N-$(C_1\text{-}C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D) proline or ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes.

7. The compound according to Claim 1, [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12α-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide p-toluenesulfonate (1:1); [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-methylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-methylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-

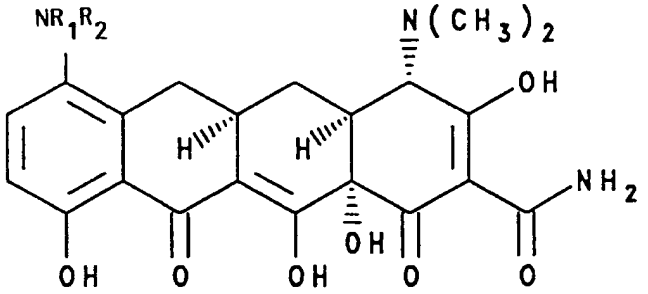
naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

8. The compound according to Claim 4, [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1);[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-9-nitro-1-11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide.

9. A method of producing a compound of the formula:



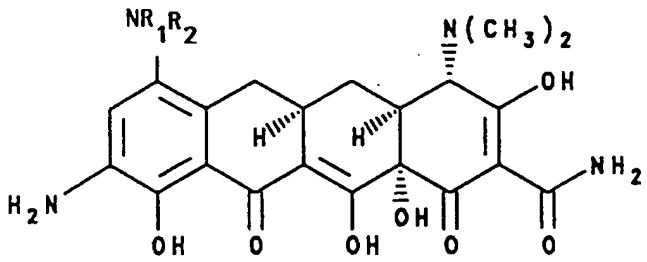
according to Claim 4, which comprises reacting a 7-(substituted amino)-6-demethyl-6-deoxytetracycline of the formula:



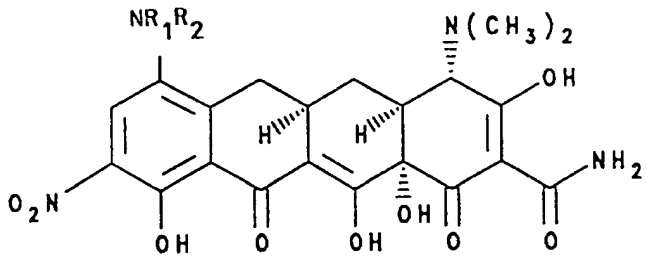
with a metal nitrate salt or nitric acid in a strong acid at -5 °C to +5 °C.

10. The process according to Claim 9 wherein said strong acid is selected from sulfuric acid, trifluoroacetic acid, methanesulfonic acid or perchloric acid.

11. A method of producing a compound of the formula:



according to Claim 1, which comprises reacting a compound of the formula:



according to Claim 4, with a reducing agent.

12. The process according to Claim 11, wherein said reducing agent comprises hydrogen in an acidic 2-methoxyethanol solvent, in the presence of a suitable catalyst; stannous chloride; soluble metal sulfide in alcoholic solvents; an active metal in mineral acid; active metal couples; a supported catalyst and a transfer hydrogenation reagent; a primary or secondary amine in the presence of formaldehyde.

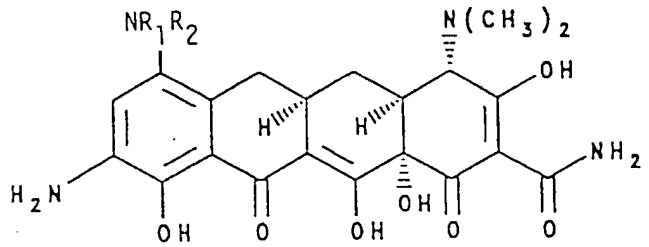
13. Use of a compound according to Claim 1 for the preparation of a medicament for the prevention, treatment or control of bacterial infections in warm-blooded animals.

14. A pharmaceutical composition of matter comprising a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.

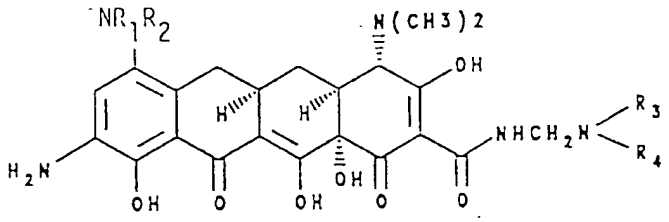
15. A veterinary composition which comprises a pharmacologically effective amount of a compound according to Claim 1 and pharmaceutically acceptable carrier.

Claims for the following Contracting States : ES, GR

1. A method of producing a compound of the formula (I) or (II):



(I)



(II)

wherein:

when R_1 = hydrogen,

R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R_1 = methyl or ethyl,

R_2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = n-propyl,

R_2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = 1-methylethyl,

R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R_1 = n-butyl,

R_2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

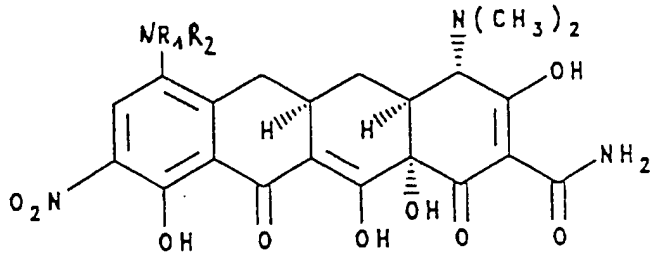
and when R_1 = 1-methylpropyl,

R_2 = 2-methylpropyl;

R_3 is selected from hydrogen, straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)-aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $-(CH_2)_nCOOR_5$ when n = 1-4 and R_5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; or (C_6-C_{10})aryl group;

R_4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group; (C_6-C_{10})aryl group; (C_7-C_9)-aralkyl group; a heterocycle group selected from 2 or 3-furanyl, 2 or 3-thienyl, 2,3 or 4-pyridyl, di(C_1-C_3)alkyl substituted pyridyl, benzofuranyl, benzothienyl, quinolinyl or $-(CH_2)_nCOOR_6$ when n = 1-4 and R_6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl; or (C_6-C_{10})aryl; or R_3 and R_4 taken together are $-(CH_2)_2W(CH_2)_2-$, wherein W is selected from $(CH_2)_n$ and n = 0-1, -NH, -N(C_1-C_3)alkyl, -N-(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from

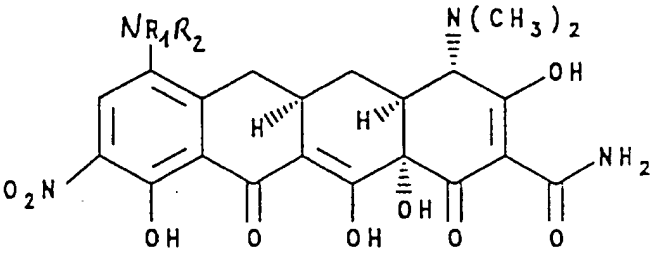
(L or D) proline, ethyl (L or D) prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts and metal complexes, which comprises reacting a compound of the formula



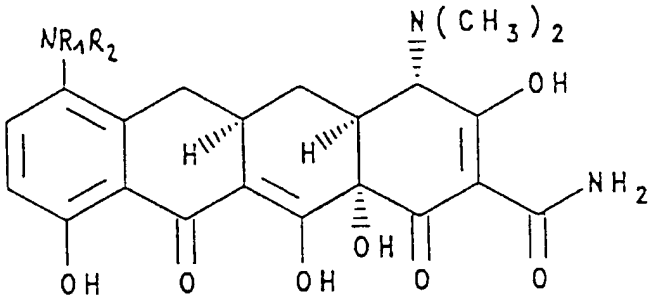
wherein R_1 and R_2 are as defined above, with a reducing agent, and, optionally, a selective N-alkylation to obtain a compound of formula (II).

2. The process according to Claim 1, wherein said reducing agent comprises hydrogen in an acidic 2-methoxyethanol solvent, in the presence of a suitable catalyst; stannous chloride; soluble metal sulfide in alcoholic solvents; an active metal in mineral acid; active metal couples; a supported catalyst and a transfer hydrogenation reagent; a primary or secondary amine in the presence of formaldehyde.

3. A method of producing a compound of the formula



wherein R_1 and R_2 are as defined in Claim 1, which comprises reacting a 7-(substituted amino)-6-demethyl-6-deoxytetracycline of the formula



with a metal nitrate salt or nitric acid in a strong acid at -5 °C to +5 °C.

4. The process according to Claim 3 wherein said strong acid is selected from sulfuric acid, trifluoroacetic acid, methanesulfonic acid or perchloric acid.

5. The method according to Claim 1 which produces [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12α-

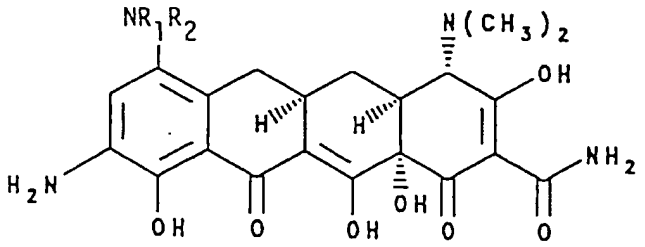
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide p-toluenesulfonate (1:1); [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-methylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-methylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

6. The method according to Claim 3 which produces [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1);[4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1); [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-9-nitro-1-11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide.

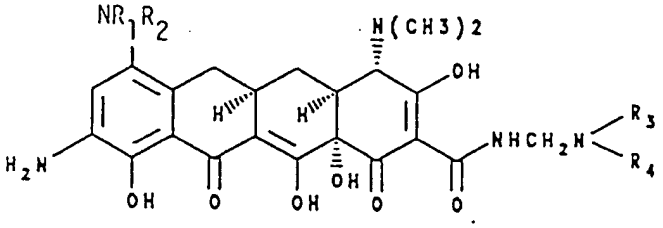
Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IE, IT, LI, LU, NL, PT, SE

1. Verbindung der Formel (I) oder (II):



(I)



(II)

worin:

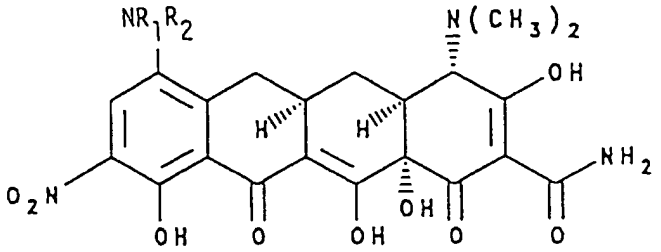
wenn R_1 = Wasserstoff, R_2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl;
und, wenn R_1 = Methyl oder Ethyl, R_2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; und, wenn R_1 = n-Propyl, R_2 = n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl,
und, wenn R_1 = 1-Methylethyl, R_2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = n-Butyl, R_2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = 1-Methylpropyl, R_2 = 2-Methylpropyl;
R_3 ist ausgewählt aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
R_4 ist ausgewählt aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstoff, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe.

2. Verbindung nach Anspruch 1, worin:
wenn R_1 = Wasserstoff, R_2 = Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl; und, wenn R_1 = Methyl, R_2 = Methyl, Ethyl, n-Propyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = Ethyl, R_2 = Ethyl, n-Propyl, n-Butyl oder 2-Methylpropyl;

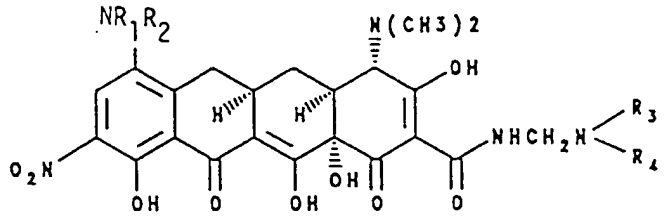
und, wenn R_1 = n-Propyl, R_2 = n-Propyl, n-Butyl oder 2-Methylpropyl;
und, wenn R_1 = n-Butyl, R_2 = n-Butyl oder 2-Methylpropyl;
R_3 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
R_4 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstoff, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe.

3. Verbindung nach Anspruch 1, worin:
wenn R_1 = Wasserstoff, R_2 = Ethyl, n-Propyl oder 1-Methylethyl; und, wenn R_1 = Methyl, R_2 = Methyl, Ethyl oder n-Propyl;
und, wenn R_1 = Ethyl, R_2 = Ethyl,
R_3 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe, R_4 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe,
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstoff, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe.

4. Verbindung der Formel (I) oder (II):



(I)



(II)

worin:
wenn R_1 = Wasserstoff, R_2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl;
und, wenn R_1 = Methyl oder Ethyl, R_2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; und, wenn R_1 = n-Propyl, R_2 = n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = 1-Methylethyl, R_2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = n-Butyl, R_2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = 1-Methylpropyl, R_2 = 2-Methylpropyl;
R_3 ist ausgewählt aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
R_4 ist ausgewählt aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstoff, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe.

5. Die Verbindung nach Anspruch 4, worin:
wenn R_1 = Wasserstoff, R_2 = Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl; und, wenn R_1 = Methyl, R_2 = Methyl, Ethyl, n-Propyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;
und, wenn R_1 = Ethyl, R_2 = Ethyl, n-Propyl, n-Butyl oder 2-Methylpropyl;
und, wenn R_1 = n-Propyl, R_2 = n-Propyl, n-Butyl oder 2-Methylpropyl;
und, wenn R_1 = n-Butyl, R_2 = n-Butyl oder 2-Methylpropyl;

R_3 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
R_4 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstof, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe.

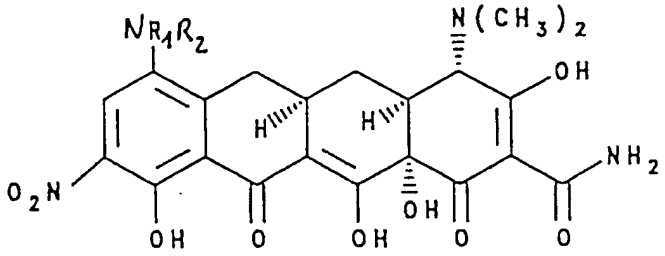
6. Verbindung nach Anspruch 4, worin:
wenn R_1 = Wasserstoff, R_2 = Ethyl, n-Propyl oder 1-Methylethyl;
und, wenn R_1 = Methyl, R_2 = Methyl, Ethyl oder n-Propyl;
und, wenn R_1 = Ethyl, R_2 = Ethyl,
R_3 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe,
R_4 ist ausgewählt aus geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe,
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstoff, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe.

7. Verbindung nach Anspruch 1, [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Hydrochlorid (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-p-Toluolsulfonat (1:1); [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:2); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-teträhydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-teträhydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid.

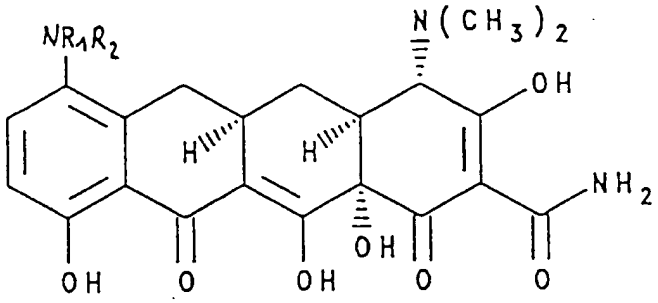
8. Verbindung nach Anspruch 4, [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:2); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-

Sulfat (1:1); [4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid.

9. Verfahren zum Herstellen einer Verbindung der Formel:



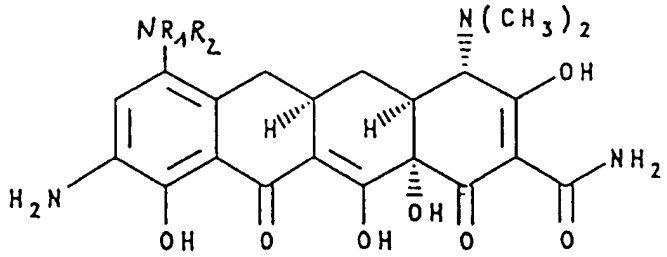
nach Anspruch 4, umfassend das Umsetzen eines 7-(substituierten Amino)-6-Desmethyl-6-desoxytetracyclins der Formel:



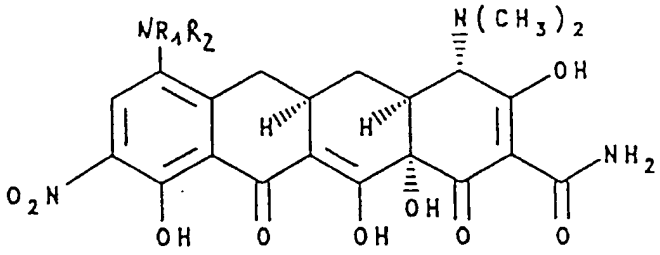
mit einem Metallnitratsalz oder Salpetersäure in einer starken Säure bei -5 °C bis +5 °C.

10. Verfahren nach Anspruch 9, worin die starke Säure ausgewählt ist aus Schwefelsäure, Trifluoressigsäure, Methansulfonsäure oder Perchlorsäure.

11. Verfahren zum Herstellen einer Verbindung der Formel:



nach Anspruch 1, umfassend das Umsetzen einer Verbindung der Formel:



gemäß Anspruch 4, mit einem Reduktionsmittel.

12. Verfahren nach Anspruch 11, worin das Reduktionsmittel Wasserstoff in einem sauren 2-Methoxyethanol-Lösungsmittel in Gegenwart eines geeigneten Katalysators, Zinn(II)chlorid, lösliches Metallsulfid in alkoholischen Lösungsmitteln, ein aktives Metall in Mineralsäure, Paarungen bzw. Verbindungen aktiven Metalls, Trägerkatalysator und ein Transfer-Hydrierungsmittel, ein primäres oder sekundäres Amin in Gegenwart von Formaldehyd, umfaßt.

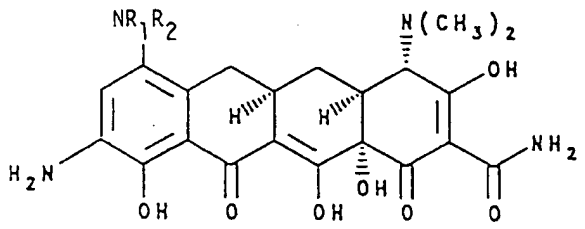
13. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Verhinderung, Behandlung oder Bekämpfung bakterieller Infektionen in warmblütigen Tieren.

14. Pharmazeutische Zubereitung, umfassend eine Verbindung nach Anspruch 1 zusammen mit einem pharmazeutisch akzeptablen Träger.

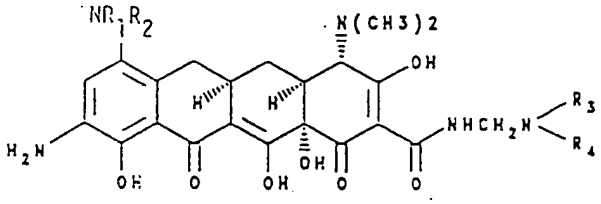
15. Veterinärzubereitung, umfassend eine pharmakologisch wirksame Menge einer Verbindung nach Anspruch 1 und einen pharmazeutisch akzeptablen Träger.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zum Herstellen einer Verbindung der Formel (I) oder (II):



(I)



(II)

worin:

wenn R_1 = Wasserstoff, R_2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl;

und, wenn R_1 = Methyl oder Ethyl, R_2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; und, wenn R_1 = n-Propyl, R_2 = n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl,

und, wenn R_1 = 1-Methylethyl, R_2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;

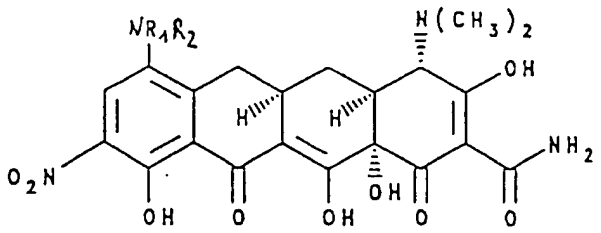
und, wenn R_1 = n-Butyl, R_2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl;

und, wenn R_1 = 1-Methylpropyl, R_2 = 2-Methylpropyl;

R_3 ist ausgewählt aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_5$, wenn n = 1-4 und R_5 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;

R_4 ist ausgewählt aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe, C_6-C_{10}-Arylgruppe, C_7-C_9-Aralkylgruppe, einer heterocyclischen Gruppe, ausgewählt aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, Di(C_1-C_3)alkyl-substituiertem Pyridyl, Benzofuranyl, Benzothienyl, Chinolinyl oder $-(CH_2)_nCOOR_6$, wenn n = 1-4 und R_6 ausgewählt ist aus Wasserstoff, geradkettiger oder verzweigter C_1-C_3-Alkylgruppe oder C_6-C_{10}-Arylgruppe;

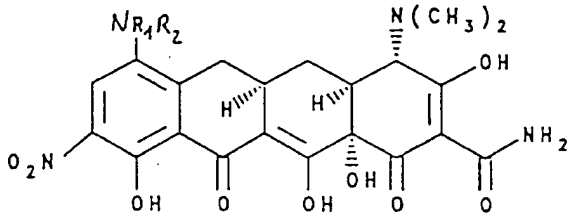
oder R_3 und R_4 sind zusammengenommen $-(CH_2)_2W(CH_2)_2-$, worin W ausgewählt ist aus $(CH_2)_n$ und n = 0 oder 1, -NH, -N(C_1-C_3)alkyl, -N(C_1-C_4)alkoxy, Sauerstoff, Schwefel oder substituierte, verwandte Verbindungen, ausgewählt aus (L- oder D-)Prolin, Ethyl(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin und die pharmakologisch akzeptablen organischen oder anorganischen Salze und Metallkomplexe, umfassend das Umsetzen einer Verbindung der Formel



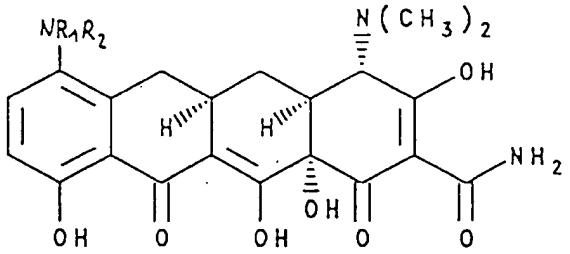
worin R_1 und R_2 die oben genannte Bedeutung haben, mit inem Reduktionsmittel und gegebenenfalls einer selektiven N-alkylierung, um eine Verbindung der Formel (II) zu erhalten.

2. Verfahren nach Anspruch 1, worin das Reduktionsmittel Wasserstoff in einem sauren 2-Methoxyethanol-Lösungsmittel in Gegenwart eines geeigneten Katalysators, Zinn(II)chlorid, lösliches Metallsulfid in alkoholischen Lösungsmitteln, ein aktives Metall in Mineralsäure, Paarungen bzw. Verbindungen aktiven Metalls, Trägerkatalysator oder ein Transfer-Hydrierungsmittel, ein primäres oder sekundäres Amin in Gegenwart von Formaldehyd, umfaßt.

3. Verfahren zum Herstellen einer Verbindung der Formel:



worin R_1 und R_2 die in Anspruch 1 angegebene Bedeutung haben, umfassend das Umsetzen eines 7-(substituierten Amino)-6-Desmethyl-6-desoxytetracyclins der Formel:



mit einem Metallnitratsalz oder Salpetersäure in einer starken Säure bei -5 °C bis +5 °C.

4. Verfahren nach Anspruch 3, worin die starke Säure ausgewählt ist aus Schwefelsäure, Trifluoressigsäure, Methansulfonsäure oder Perchlorsäure.

5. Verfahren nach Anspruch 1, das herstellt [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Hydrochlorid (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-p-Toluolsulfonat (1:1); [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naph-thacencarboxamid-Sulfat (1:2); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-9-Amino-4-(dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-

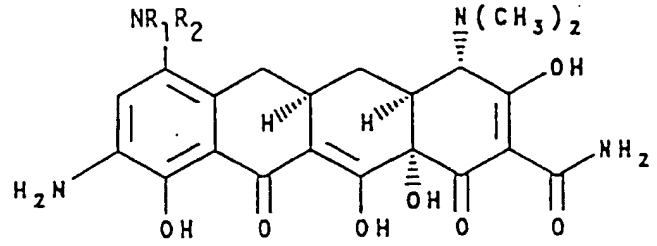
octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacencarboxamid.

6. Verfahren nach Anspruch 3, das erzeugt [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:2); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid-Sulfat (1:1); [4S-(4α,12aα)]-4,7-bis-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-4-(Dimethylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid; [4S-(4α,12aα)]-4-(Dimethylamino)-7-(ethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1-11-dioxo-2-naphthacencarboxamid.

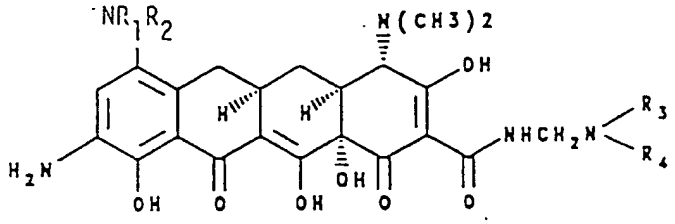
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IE, IT, LI, LU, NL, PT, SE

1. Un composé de formule (I) ou (II) :



(I)



(II)

dans laquelle :
lorsque R_1 = hydrogène,
R_2 = méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle ou 1,1-diméthyléthyle ;
et lorsque R_1 = méthyle ou éthyle,
R_2 = méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = n-propyle,
R_2 = n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = 1-méthyléthyle,
R_2 = n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;

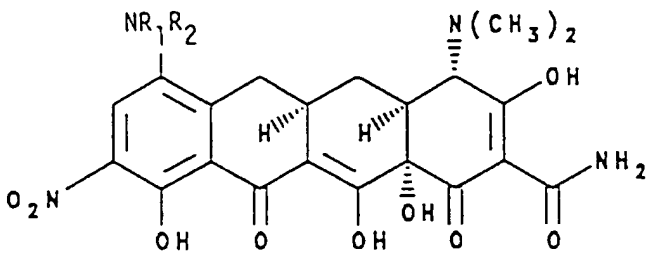
et lorsque R_1 = n-butyle,
R_2 = n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = 1-méthylpropyle,
R_2 = 2-méthylpropyle ;
R_3 est choisi parmi l'hydrogène, un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; un groupe hétérocyclique choisi parmi les suivants 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di(C_1-C_3)alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou - $(CH_2)_nCOOR_5$ lorsque n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou un groupe (C_6-C_{10})aryle ;
R_4 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di(C_1-C_3)alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou - $(CH_2)_nCOOR_6$ lorsque n = 1-4 et R_6 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou un groupe (C_6-C_{10})aryle ; ou bien R_3 et R_4 pris ensemble désignent $-(CH_2)_2W-(CH_2)_2-$, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, -N(C_1-C_3)alkyle, -N(C_1-C_4)alcoxy, oxygène, soufre ou des congénères substitués choisis parmi la (L ou D) proline, le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques.

2. Le composé selon la revendication 1, selon laquelle :
lorsque R_1 = hydrogène,
R_2 = éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle ou 1,1-diméthyléthyle ;
et lorsque R_1 = méthyle,
R_2 = méthyle, éthyle, n-propyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = éthyle,
R_2 = éthyle, n-propyle, n-butyle ou 2-méthylpropyle ;
et lorsque R_1 = n-propyle,
R_2 = n-propyle, n-butyle ou 2-méthylpropyle ;
et lorsque R_1 = n-butyle,
R_2 = n-butyle ou 2-méthylpropyle ;
R_3 est choisi parmi un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di(C_1-C_3)alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou -$(CH_2)_nCOOR_5$ lorsque n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou bien un groupe (C_6-C_{10})aryle ;
R_4 est choisi parmi un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di(C_1-C_3)alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou - $(CH_2)_nCOOR_6$ lorsque n = 1-4 et R_6 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou (C_6-C_{10})aryle ; ou bien R_3 et R_4 pris ensemble désirent $-(CH_2)_2W(CH_2)_2-$, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, -N(C_1-C_3)alkyle, -N(C_1-C_4)alcoxy, oxygène, soufre ou des congénères substitués choisis parmi la (L ou D) proline ou le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques.

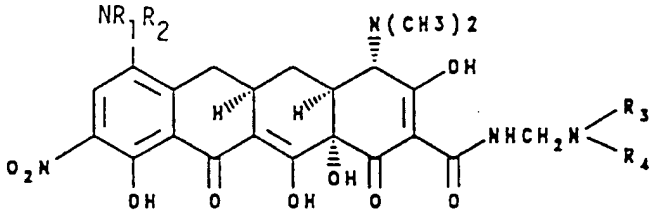
3. Le composé selon la revendication 1, selon laquelle :
lorsque R_1 = l'hydrogène,
R_2 = éthyle, n-propyle ou 1-méthyléthyle ;
et lorsque R_1 = méthyle,
R_2 = méthyle, éthyle ou n-propyle ;
et lorsque R_1 = éthyle,
R_2 = éthyle ;
R_3 est choisi parmi un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; ou -$(CH_2)_nCOOR_5$ lorsque n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou un groupe (C_6-C_{10})aryle ;
R_4 est choisi parmi un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; ou -$(CH_2)_nCOOR_6$ lorsque n = 1-4 ;

R_5 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou un groupe (C_6-C_{10})-aryle ; ou bien R_3 et R_4 pris ensemble désignent -$(CH_2)_2W(CH_2)_2$-, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, -N(C_1-C_3)alkyle, -N(C_1-C_4)alcoxy, oxygène, soufre ou des congénères substitués choisis parmi la (L ou D) proline ou le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques.

4. Un composé de formule (I) ou (II) :



(I)



(II)

dans laquelle :
lorsque R_1 = hydrogène,
R_2 = méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle ou 1,1-diméthyléthyle ;
et lorsque R_1 = méthyle ou éthyle,
R_2 = méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = n-propyle,
R_2 = n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = 1-méthyléthyle,
R_2 = n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = n-butyle,
R_2 = n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = 1-méthylpropyle,
R_2 = 2-méthylpropyle ;
R_3 est choisi parmi l'hydrogène, un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle ; un groupe (C_7-C_9)aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle ; 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di(C_1-C_3)alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou -$(CH_2)_nCOOR_5$ où n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou un groupe (C_6-C_{10})aryle ;
R_4 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; un groupe (C_6-C_{10})aryle; un groupe (C_7-C_9)aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di(C_1-C_3)alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou - $(CH_2)_nCOOR_6$ lorsque n = 1-4 et R_6 est choisi parmi l'hydrogène ; un groupe (C_1-C_3)alkyle linéaire ou ramifié ; ou un groupe (C_6-C_{10})aryle ; ou bien R_3 et R_4 pris ensemble désirent -$(CH_2)_2$-W-$(CH_2)_2$-, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, -N(C_1-C_3)alkyle, -N(C_1-C_4)alcoxy, oxygène,

soufre ou des congénères substitués choisis parmi la (L ou D) proline, le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques.

5. Le composé selon la revendication 4, selon laquelle
lorsque R_1 = l'hydrogène,
R_2 = éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle ou 1,1-diméthyléthyle ;
et lorsque R_1 = méthyle,
R_2 = méthyle, éthyle, n-propyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = éthyle,
R_2 = éthyle, n-propyle, n-butyle ou 2-méthylpropyle ;
et lorsque R_1 = n-propyle,
R_2 = n-propyle, n-butyle ou 2-méthylpropyle ;
et lorsque R_1 = n-butyle,
R_2 = n-butyle ou 2-méthylpropyle ;
R_3 est choisi parmi un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; un groupe $(C_6\text{-}C_{10})$aryle ; un groupe $(C_7\text{-}C_9)$aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di$(C_1\text{-}C_3)$alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou -$(CH_2)_nCOOR_5$ lorsque n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; ou un groupe $(C_6\text{-}C_{10})$aryle ; R_4 est choisi parmi un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; un groupe $(C_6\text{-}C_{10})$aryle ; un groupe $(C_7\text{-}C_9)$aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di$(C_1\text{-}C_3)$alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou -$(CH_2)_nCOOR_6$ lorsque n = 1-4 et R_6 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; ou un groupe $(C_6\text{-}C_{10})$aryle ; ou bien R_3 et R_4 pris ensemble désignent -$(CH_2)_2W(CH_2)_2$-, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, -N$(C_1\text{-}C_3)$alkyle, -N$(C_1\text{-}C_4)$alcoxy, oxygène, soufre ou des congénères substitués choisis parmi la (L ou D) proline ou le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques.

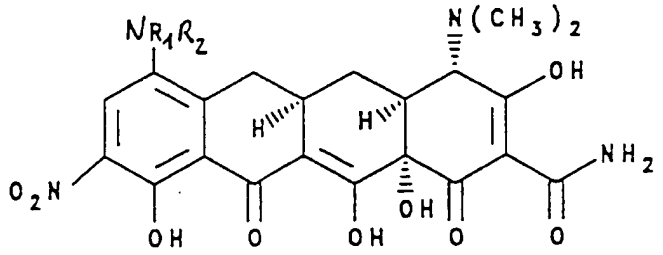
6. Le composé selon la revendication 4, selon laquelle
lorsque R_1 = hydrogène,
R_2 = éthyle, n-propyle ou 1-méthyléthyle ;
et lorsque R_1 = méthyle,
R_2 = méthyle, éthyle ou n-propyle ;
et lorsque R_1 = éthyle,
R_2 = éthyle ;
R_3 est choisi parmi un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; un groupe $(C_6\text{-}C_{10})$aryle ; un groupe $(C_7\text{-}C_9)$aralkyle ; ou -$(CH_2)_nCOOR_5$ lorsque n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; ou un groupe $(C_6\text{-}C_{10})$aryle ;
R_4 est choisi parmi un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; un groupe $(C_6\text{-}C_{10})$aryle ; un groupe $(C_7\text{-}C_9)$aralkyle ; ou -$(CH_2)_nCOOR_6$ lorsque n = 1-4 et
R_6 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; ou un groupe $(C_6\text{-}C_{10})$-aryle ; ou bien R_3 et R_4 pris ensemble désignent -$(CH_2)_2W(CH_2)_2$-, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, - N$(C_1\text{-}C_3)$alkyle, -N$(C_1\text{-}C_4)$alcoxy, oxygène, soufre ou des congénères substitués choisis parmi la (L ou D) proline ou le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques.

7. Le composé selon la revendication 1, à savoir le suivant : [4S-(4α,12aα)]-9-amino)-4,7-bis-(diméthyléthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1); [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12α-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, chlorhydrate (1:1) ; [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-1,4,4a,5,5a,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphta cènecarboxamide, p-toluènesulfonate (1:1) ; [4S-(4α,12α)]-9-amino-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:2) ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthyl-méthylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-[(1-méthyléthyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-

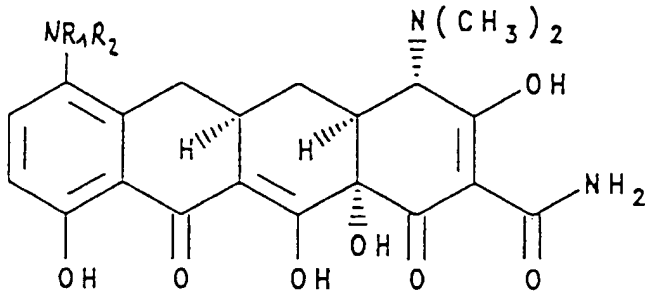
3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4,7-bis-(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-7-(diéthylamino)-4-(diméthylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthylméthylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-[(1-méthyléthyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide.

8. Le composé selon la revendication 4 qui est le suivant : [4S-(4α, 12aα)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:2) ; [4S-(4α,12aα)]-4-(diméthylamino)-7-(éthylméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydro-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4s-(4α,12aα)]-4-(diméthylamino)-7-[(1-méthyléthyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α, 12aα)]-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3, 10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-4-(diméthylamino)-7-(éthylméthylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tétrahydro-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-4-(diméthylamino)-7-[(1-méthyléthyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1, 11-dioxo-2-naphtacènecarboxamide.

9. Une méthode de production d'un composé de formule :



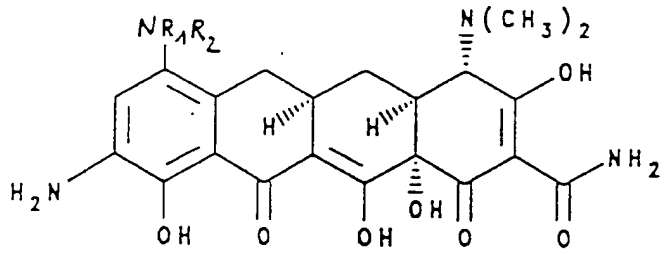
selon la revendication 4, qui comprend la réaction d'un 7-(amino substitué)-6-déméthyl-6-désoxytétracycline de formule :



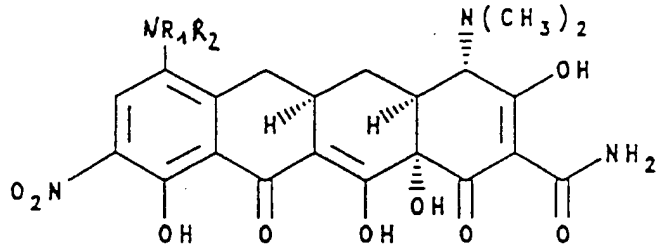
avec un sel nitrate métallique ou l'acide nitrique dans un acide fort à -5°C à +5°C.

10. Le procédé selon la revendication 9, selon laquelle ledit acide fort est choisi parmi l'acide sulfurique, l'acide trifluoroacétique, l'acide méthanesulfonique ou l'acide perchlorique.

11. Une méthode de production d'un composé de formule :



selon la revendication 1, qui comprend la réaction d'un composé de formule :



selon la revendication 4 avec un agent réducteur.

12. Le procédé selon la revendication 11, selon laquelle ledit agent réducteur comprend l'hydrogène dans un solvant 2-méthoxyéthanol acide, en présence d'un catalyseur approprié ; de chlorure stanneux ; de sulfure métallique soluble dans des solvants alcooliques ; d'un métal actif dans un acide minéral ; des couples de métaux actifs ; d'un catalyseur sur support et d'un réactif d'hydrogénation par transfert ; d'une amine primaire ou secondaire en présence de formaldéhyde.

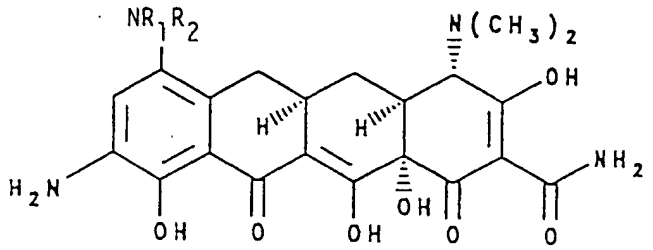
13. Utilisation d'un composé selon la revendication 1, pour la préparation d'un médicament pour la prévention, le traitement ou le contrôle des infections bactériennes chez les animaux à sang chaud.

14. Une composition pharmaceutique comprenant un composé selon la revendication 1 en association avec un support pharmaceutiquement acceptable.

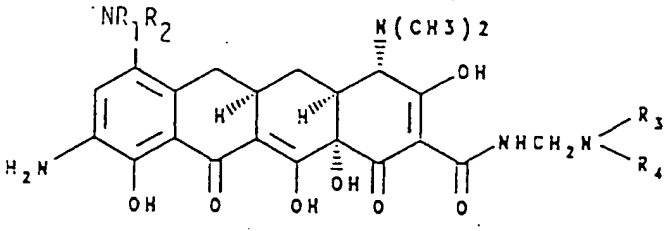
15. Une composition vétérinaire qui comprend une quantité pharmacologique efficace d'un composé selon la revendication 1 et un support pharmaceutiquement acceptable.

Revendications pour les Etats contractants suivants : ES, GR

1. Une méthode de production d'un composé de formule (I) ou (II) :

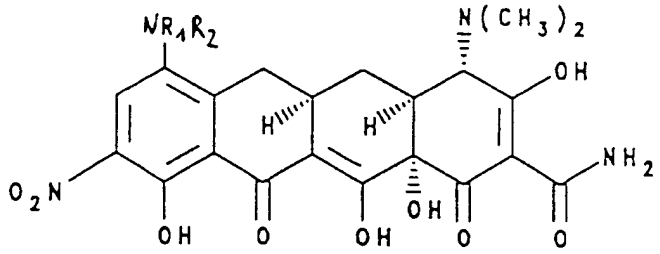


(I)



(II)

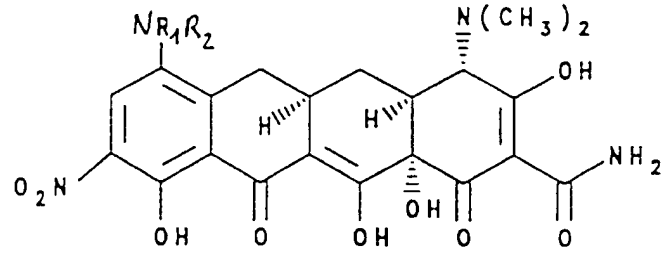
dans laquelle :
lorsque R_1 = hydrogène,
R_2 = méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle, 2-méthylpropyle ou 1,1-diméthyléthyle ;
et lorsque R_1 = méthyle ou éthyle,
R_2 = méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = n-propyle,
R_2 = n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = 1-méthyléthyle,
R_2 = n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = n-butyle,
R_2 = n-butyle, 1-méthylpropyle ou 2-méthylpropyle ;
et lorsque R_1 = 1-méthylpropyle,
R_2 = 2-méthylpropyle ;
R_3 est choisi parmi l'hydrogène, un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; un groupe $(C_6\text{-}C_{10})$aryle ; un groupe $(C_7\text{-}C_9)$aralkyle ; un groupe hétérocyclique choisi parmi les suivants 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di$(C_1\text{-}C_3)$alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou - $(CH_2)_nCOOR_5$ lorsque n = 1-4 et R_5 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; ou un groupe $(C_6\text{-}C_{10})$aryle ;
R_4 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; un groupe $(C_6\text{-}C_{10})$aryle ; un groupe $(C_7\text{-}C_9)$aralkyle ; un groupe hétérocyclique choisi parmi les suivants : 2 ou 3-furanyle, 2 ou 3-thiényle, 2,3 ou 4-pyridyle, di$(C_1\text{-}C_3)$alkyl substitué pyridyle, benzofuranyle, benzothiényle, quinolinyle ou - $(CH_2)_nCOOR_6$ lorsque n = 1-4 et R_6 est choisi parmi l'hydrogène ; un groupe $(C_1\text{-}C_3)$alkyle linéaire ou ramifié ; ou un groupe $(C_6\text{-}C_{10})$aryle ; ou bien R_3 et R_4 pris ensemble désignent $-(CH_2)_2W-(CH_2)_2-$, où W est choisi parmi $(CH_2)_n$ et n = 0-1, -NH, -N$(C_1\text{-}C_3)$alkyle, -N$(C_1\text{-}C_4)$alcoxy, oxygène, soufre ou des congénères substitués choisis parmi la (L ou D) proline, le (L ou D) prolinate d'éthyle, la morpholine, la pyrrolidine ou la pipéridine ; et les sels organiques et inorganiques pharmacologiquement acceptables et les complexes métalliques qui comprend la réaction de composé de formule :



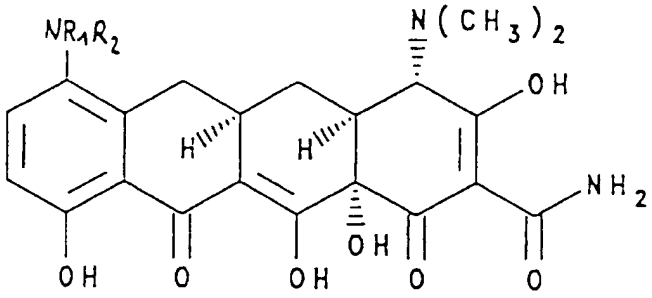
dans laquelle R_1 et R_2 sont comme définis précédemment, avec un agent réducteur et, éventuellement, une N-alkylation sélective pour obtenir un composé de formule (II).

2. Le procédé selon la revendication 1, selon laquelle ledit agent réducteur comprend de l'hydrogène dans un solvant 2-méthoxyéthanol acide, en présence d'un catalyseur approprié ; le chlorure stanneux ; un sulfure métallique soluble dans les solvants alcooliques ; un métal actif dans un acide minéral ; des couples de métaux actifs ; un catalyseur sur support et un réactif d'hydrogénation par transfert ; une amine primaire ou secondaire en présence de formaldéhyde.

3. Une méthode de production d'un composé de formule :



dans laquelle R_1 et R_2 sont comme définis dans la revendication 1, qui comprend la réaction d'une 7-(amino substitué)-6-déméthyl-6-désoxytétracycline de formule



avec un sel nitrate métallique ou avec l'acide nitrique dans un acide fort à -5 °C à +5 °C.

4. Le procédé selon la revendication 3, selon laquelle ledit acide fort est choisi parmi l'acide sulfurique, l'acide trifluoroacétique, l'acide méthanesulfonique et l'acide perchlorique.

5. La méthode selon la revendication 1 qui produit les composés suivants : [4S-(4α,12aα)]-9-amino)-4,7-bis(diméthyléthylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-oc-

tahydro-3,10,12α-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, chlorhydrate (1:1) ; [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-1,4,4a,5,5a,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, p-toluènesulfonate (1:1) ; [4S-(4α,12α)]-9-amino-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:2) ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthyl-méthylamino)-1,4,4a, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-[(1-méthyléthyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthyl-méthylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-[(1-méthyléthyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-9-amino-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide.

6. La méthode selon la revendication 3 qui produit les composés suivants : [4S-(4α, 12aα)]-4,7-bis-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:2) ; [4S-(4α,12aα)]-4-(diméthylamino)-7-(éthylméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydro-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4s-(4α,12aα)]-4-(diméthylamino)-7-[(1-méthyléthyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α, 12aα)]-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide, sulfate (1:1) ; [4S-(4α,12aα)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-4-(diméthylamino)-7-(éthylméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydro-9-nitro-1,11-dioxo-2-naphtacènecarboxamide;[4S-(4α,12aα)]-4-(diméthylamino)-7-[(1-méthyléthyl)-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide ; [4S-(4α,12aα)]-4-(diméthylamino)-7-(éthylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-nitro-1,11-dioxo-2-naphtacènecarboxamide.